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UNSATURATED 4H-1,3-OXAZINES (REVIEW)

I. P. Yakovlev, A. V. Prep'yalov, and B. A. Ivin

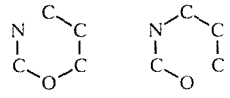
Data on the methods of production, chemical properties, and biological activity of unsaturated 4H-1,3-oxazines are generalized.

Unsaturated 1,3-oxazines, which have been the object of persistent interest for the past three decades, still remain little-studied compounds. The available literature data on the methods of synthesis, structure and properties of these substances are unsystematic and sometimes simply contradictory. At the same time, it has already been established that a number of derivatives of unsaturated 1,3-oxazines possess valuable practical properties, in particular, pronounced biological activity.

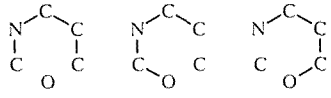
The aim of this review is a generalization of the data published up to 1990 on the chemistry and biological activity of unsaturated 4H-1,3-oxazines. We hope that this work will be of definite interest for researchers concerned with azines in generally and 1,3-oxazines in particular, since it is a logical continuation of the excellent review, devoted to unsaturated 6H-1,3-oxazines, that recently appeared in print [1].

We divided the methods of producing the compounds under discussion into the four traditional methods of synthesis of six-membered heterocycles, depending on the number of atoms contained in the initial fragments of the future ring [2] (Scheme 1). For convenience of systematization of the material presented, syntheses proceeding with expansion of the ring were classified as (5 + 1), type B reactions.

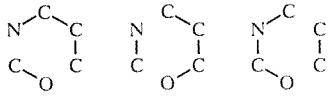
Scheme 1



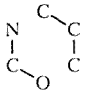
Type A
(6+0)



Type B
(5+1)



Type C
(4+2)



Type D
(3+3)

METHODS

1. Reactions (6 + 0)

Insofar as we know, reactions of this type have not been widely used for the synthesis of 4H-1,3-oxazines. Noteworthy is a method of production of the oxazinone II by cyclization of the Schiff base I in boiling xylene [3] and condensation of N-acylamides of β-ketoacids III with P_2O_5 at 100°C, leading to the oxazines IV [4].

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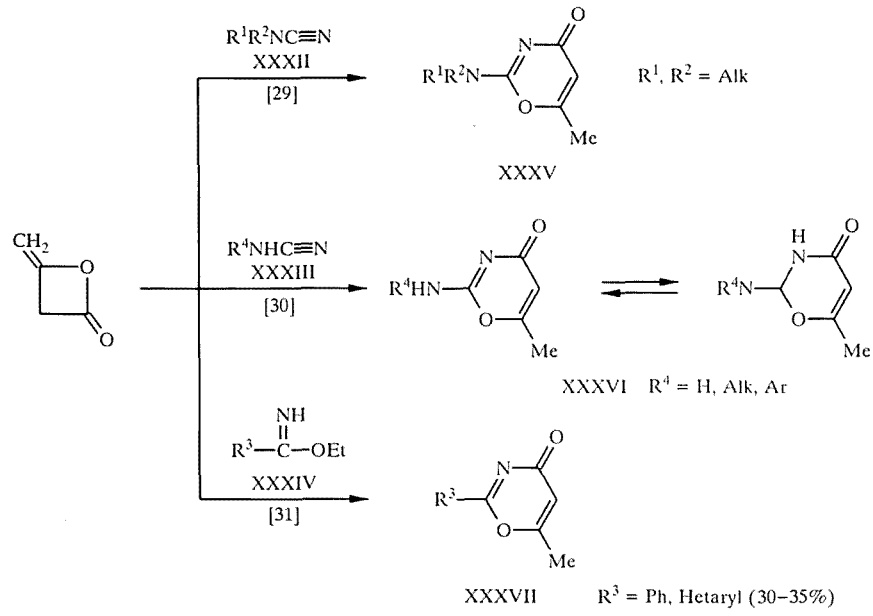
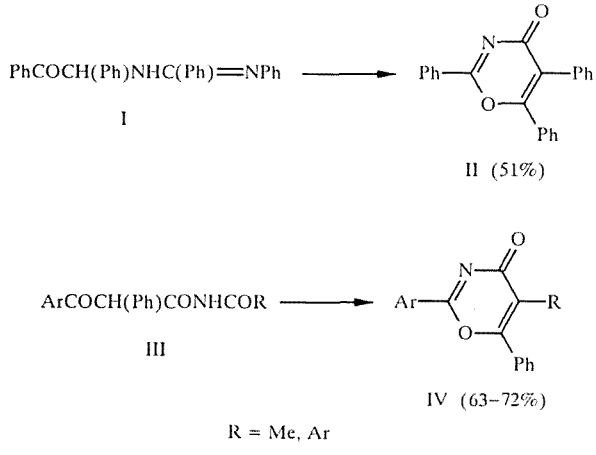
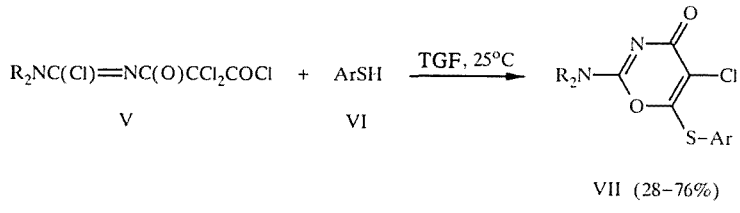
Scheme 2



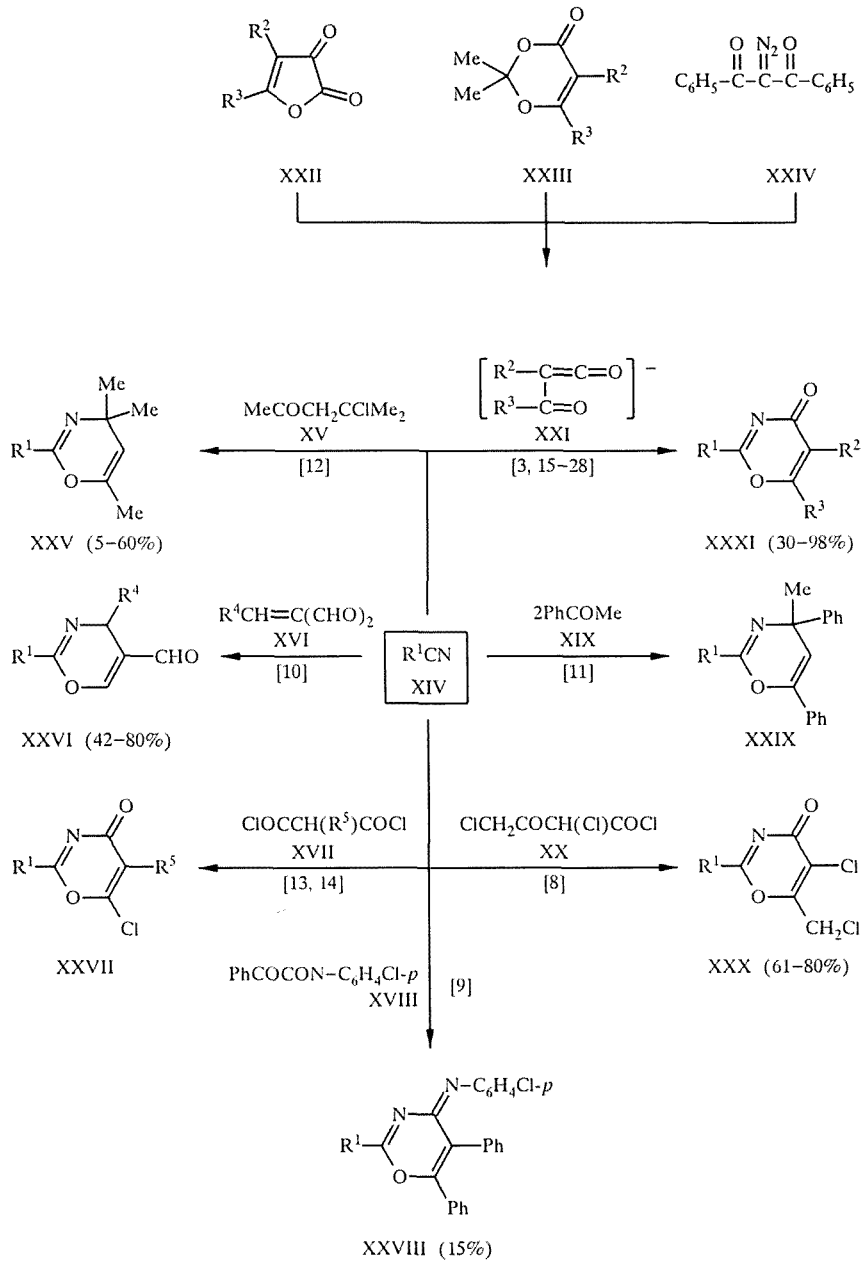


The method of production of oxazinones VII by the reaction of compound V with thiophenols VI [5] should also be assigned to this reaction type.



Many syntheses proceeding with the formation of intermediates similar to compounds I and III belong to types B–D and will be examined below.

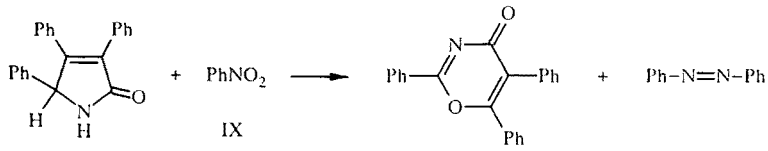
Scheme 3



R^1 = Alk, Ar, Acyl, Alk_2N, $(PhCH_2)_2N$, PhO, PhCONH, NHC(=NH)NHPh; R^2 = H, Alk, Ar; R^3 = H, Alk, AlkO, Ar, Hal; R^4 = Ar; R^5 = Alk, Ar

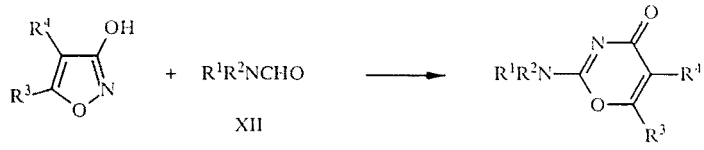
2. Reactions (5 + 1)

Reactions of this type also have not found wide use in the synthesis of 1,3-oxazines. Only a few reactions, which proceed with expansion of the ring, can be assigned to it. Thus, the authors of [6], oxidizing the pyrrolinone VIII with nitrobenzene IX, obtained triphenyloxazinone II in a yield of 50%.



VIII IX II

Derivatives of 2-amino-4H-1,3-oxazin-4-ones (XIII) were produced under mild conditions, in a rather high yield, by heating the oxazoles XI with the formamides XII in toluene at 50°C in the presence of trimethyl- or triethylamine [7].

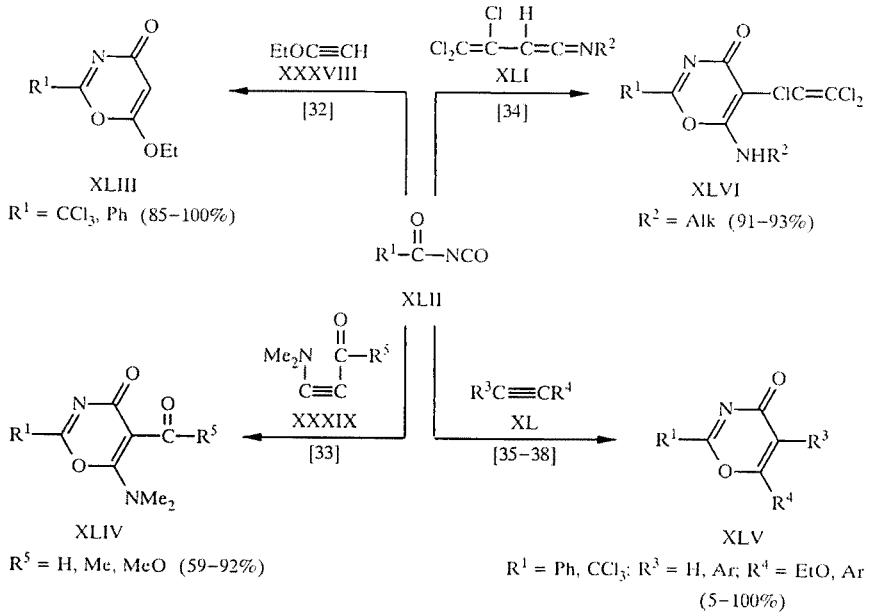


XI XII XIII

R^1 = Alk; R^2 = Alk, Ar; R^3 = R^4 = H, Hal, Alk, Ar

3. Reactions (4 + 2)

These systems are the most widely used for constructing the ring of unsaturated 4H-1,3-oxazines. Compounds with carbon–carbon or carbon–nitrogen multiple bonds, which play the role of the "two-membered" component, and carbonyl compounds, which play the role of the "four-membered" component, are frequently used as starting materials. Reactions of nitriles XIV with carbonyl compounds XV-XIX, as well as with acylketenes XX, generated in situ from substances XXI-XXIII, leading to the oxazinones XXIV-XXXI (see Scheme 3), have been widely developed in recent years [3, 8-28].



XLIII
R^1 = CCl_3, Ph (85–100%)

XLIV
R^5 = H, Me, MeO (59–92%)

XLV
R^1 = Ph, CCl_3; R^3 = H, Ar; R^4 = EtO, Ar (5–100%)

XLVI
R^2 = Alk (91–93%)

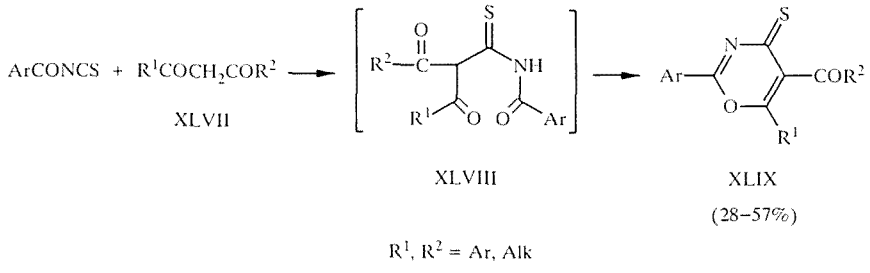
XLII

In similar reactions with the nitriles XXXII and XXXIII and iminoesters XXXIV, diketene is often used as the "four-membered" component [29-31]. This pathway is a convenient method of synthesis of 2-substituted oxazinones XXXV-XXXVII (Scheme 2).

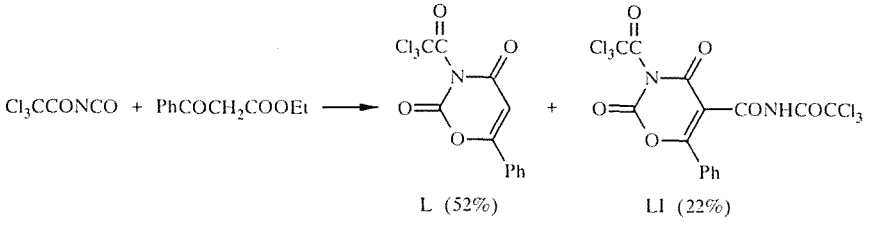
The methods shown (Schemes 2, 3) for the production of the oxazines under discussion are extremely attractive in the availability of the starting materials, high yield of the end products, and technological feasibility.

Reactions of cycloaddition of acetylene derivatives XXXVIII-XL and imines XLI to acyl isocyanates XLII may be of special interest for the synthesis of 1,3-oxazin-4-ones with reactive substituents in positions 5 and 6. Usually they proceed under mild conditions, often in the cold. The yields of the oxazines XLIII-XLVI are rather high, sometimes almost quantitative [32-38] (Scheme 4). In certain cases the structure of acyl isocyanates, in the opinion of the authors of [35-38], may have a definite influence not only on the reaction rate but also on the nature of the product formed. The causes of this are not discussed in the studies cited, possibly on account of the limited series of acyl isocyanates used. Probably we should also mention the absence of any information in the literature on reactions of this kind for acyl isothiocyanates. In our opinion, they may be not only of theoretical interest but also of practical importance as a potentially new approach for the creation of 1,3-oxazine-4-thiones. (See scheme at the bottom of the previous page.)

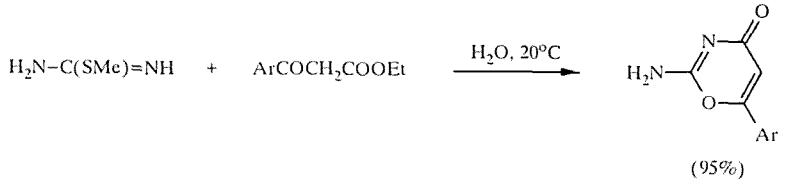
Noteworthy in connection with this is the reaction of 1,3-diketones XLVII with aroyl isothiocyanates in the presence of equimolar amounts of triethylamine. It evidently proceeds through the intermediate thioacetamide XLVIII with the formation of 2,6-disubstituted 5-acyloxazine-4-thiones (XLIX) [39].



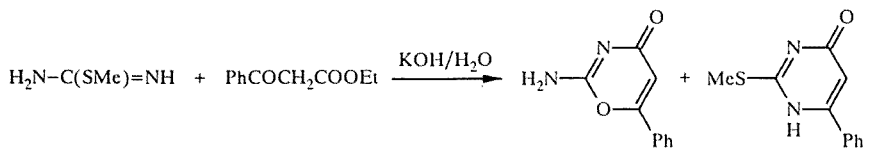
It is easy to note that in this case the aroyl isothiocyanates are donors of the "four-membered" fragment. Insofar as we know, such reactions involving acyl isocyanates have not been widely studied. The interaction of trichloroacetyl isocyanate with ethylbenzoyl acetate proceeds rather complexly, but from the nature of the oxazines L and LI formed it can be concluded that trichloroacetyl isocyanate is the donor of the "two-membered" fragment in this case [40].



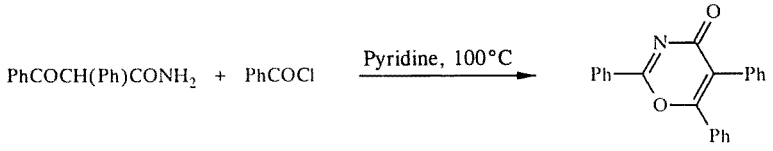
2-Amino-6-aryl-1,3-oxazin-4-ones were obtained in good yield under mild conditions by the reaction of methylthio-pseudourea with ethylaroyl acetates [41].



If methylthiopseudourea is treated with a twofold excess of benzoyl acetate in alkaline medium, then together with 2-amino-6-phenyl-1,3-oxazin-4-one, 2-methylthio-6-phenylpyrimidin-4-one is formed [42].

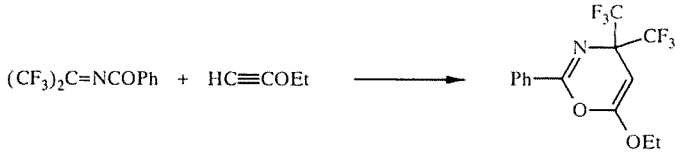


1,5,6-Triphenyl-1,3-oxazin-4-one (II) was obtained in a small yield (24%) by treatment of phenylbenzoylacetamide with benzoyl chloride [6].



II

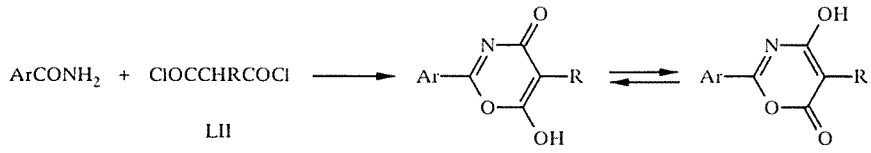
The cyclization of the benzoylimine of hexafluoroacetone and ethoxyacetylene with the formation of 2-phenyl-6-ethoxy-4,4-bis(trifluoromethyl)-1,3-4H-oxazine [43] should probably be considered as a reaction proceeding according to the [4 + 2] cycloaddition type.



(80%)

4. Reactions (3 + 3)

The interaction of amides of aromatic acids with monosubstituted malonyl chlorides LII, which, in the opinion of the authors of [44], lead to the oxazines LIII and LIV, can be assigned to this reaction type. This is supported by the results of [45] and our investigations, for example, [46].



LII

R = Alk, Ar

LIII

LIV

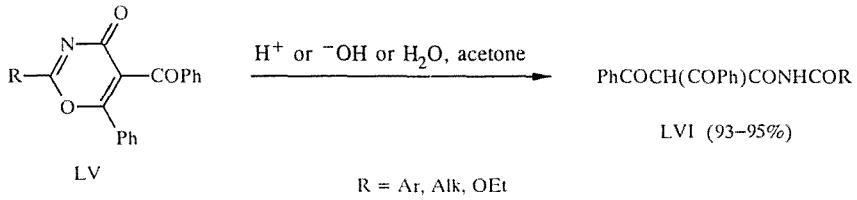
Thus, summarizing the results of an analysis of the literature data on methods of production of unsaturated 4H-1,3-oxazines, we can conclude that the main synthetic approach is the (4 + 2) cyclization reactions (type C). Among this group of reactions, the bulk of the studies have been devoted to the pathways of formation of 4-oxo-1,3-oxazines. Nonetheless, such interesting reactions in this series as the interaction of acyl iso(thio)cyanates with acetylenic hydrocarbons and that of nitriles

with malonyl chlorides, in our opinion, have received little study. The data on them are not systematic, and some results are extremely debatable and are in need of further refinement.

CHEMICAL PROPERTIES

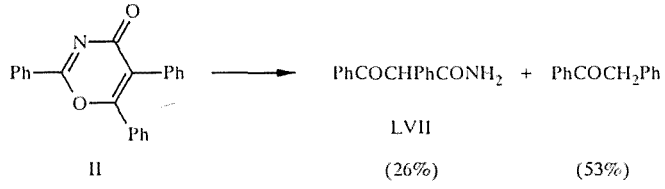
1. Reactions with O-Nucleophiles

Oxoderivatives of 1,3-oxazines possessing a C=N double bond in the ring may be considered formally as cyclic iminoesters. This explains their low hydrolytic stability to some degree. The structure of hydrolysis and alcoholysis products depends on the structure of the initial oxazines and on the reaction conditions. Thus, 1,3-oxazin-4-ones LV are hydrolyzed under mild conditions with the formation of the corresponding N-acylamides of β-ketoacids LVI [15].

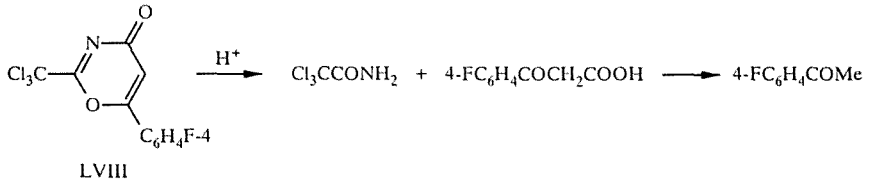


Probably the cyclization of the benzoylimine of hexafluoroacetone and ethoxyacetylene with the formation of 2-phenyl-6-ethoxy-4,4-bis(trifluoromethyl)-1,3-4H-oxazine [43] should be considered as a reaction proceeding according to the [4 + 2] cycloaddition type.

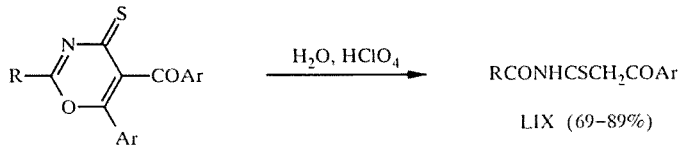
The presence of strong electron-acceptor substituents in position 2 frequently promotes not only opening of the ring but also a more profound conversion of the hydrolysis products, associated with decarboxylation and hydrolysis of the acylamino group. Thus, treatment of the oxazine II with a 20% aqueous solution of HCl in dioxane gives the amide LVII and deoxybenzoin.



Acid hydrolysis of the oxazine LVIII proceeds even more complexly. Trichloroacetamide and p-fluoroacetophenone have been isolated from the reaction mixture [35].



2,6-Disubstituted 5-acyl-4H-1,3-oxazine-4-thiones (XLIX) are hydrolyzed to N-acylaroylthioacetamides LIX in acetic acid in the presence of 50% $HClO_4$ [39].

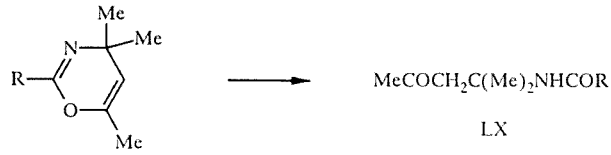


XLIX

LIX (69–89%)

R = Me, Ph

The oxazines XXV are readily cleaved in dilute solutions of acids, with a quantitative yield, forming β-acylaminoketones LX [47].

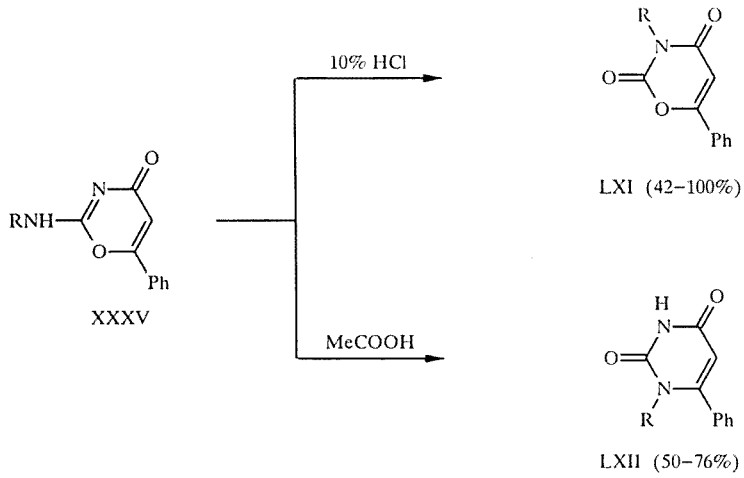


XXV

LX

R = Alk, Ar

2-Amino-1,3-oxazin-4-ones (XXXV), treated with 10% aqueous HCl, form 1,3-oxazine-2,4-diones (LXI) with a quantitative yield, and when the initial oxazines are boiled in concentrated acetic acid for 24 h, 1-substituted 6-methyluracils (LXII) are formed in a yield of 50-76% [30, 41, 42].



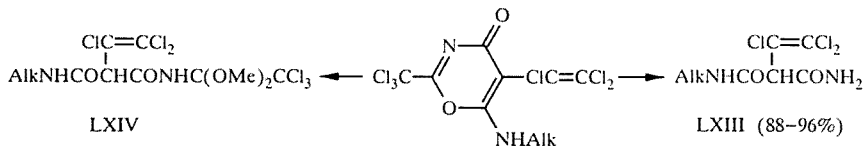
XXXV

LXI (42–100%)

LXII (50–76%)

R = H, Alk, Ar

The high lability of the oxazines under discussion is characteristic of their aqueous alcohol solutions. The oxazinones XLVI are hydrolyzed to the amides LXIII in 90% ethanol at 50°C [34]. In methanol at 18-25°C without access to atmospheric moisture, these oxazines give malonamides LXIV with a quantitative yield.

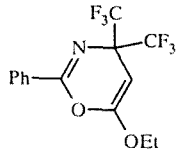


LXIV

XLVI

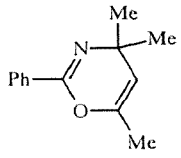
LXIII (88–96%)

2-Phenyl-6-ethoxy-4,4-bis(trifluoromethyl)-4H-1,3-oxazine, when heated in an aqueous alcohol solution of KOH, gives β-benzoylamino-β,β-bis(trifluoromethyl)propionic acid [43].



$\longrightarrow$ $PhCONHC(CF_3)_2CH_2COOH$

4,4,6-Trimethyl-2-phenyl-1,3-oxazine forms 2-benzylamino-2-methyl-4-pentanol under the action of sodium in ethanol [47].



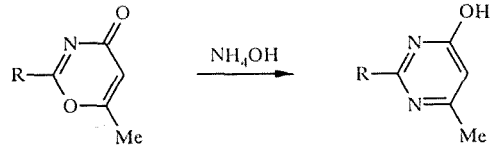
LXIII

$\longrightarrow$ $HOCH(Me)CH_2C(CH_3)_2NHCH_2Ph$ (53%)

We should mention that the hydrolysis reactions shown do not permit an unambiguous determination of the predominant direction of attack of the nucleophile. Probably it can be stated with sufficient assurance that the reaction centers in the oxazine ring are the C_2 or C_6 atoms. At the same time, the last methanolysis reaction indicates preference for attack at C_2.

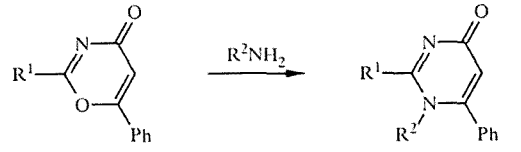
2. Reactions with N-Nucleophiles

The reaction with ionic or alcohol solutions of ammonia and primary amines, leading to the formation of oxoderivatives of pyrimidine, is one of the most widespread reactions of 4H-1,3-oxazines. In these cases too, the C_2 or C_6 atoms of the heterocycle are subjected to nucleophilic attack, followed by intramolecular cyclization of linear intermediates. Thus, 2-substituted 6-methyl-1,3-oxazinones (LXI, LXVI) with aqueous ammonia and primary amines under mild conditions give the corresponding 4-hydroxypyrimidines LXVII and LXVIII [30, 31].



LXV LXVII (62–94%)

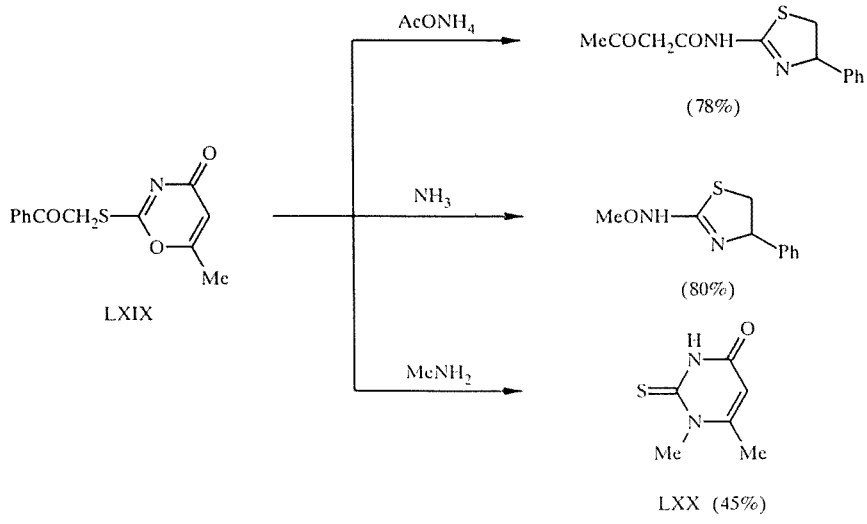
R = 2-,3-, and 4-pyridyl, $NHC(NH_2)=NH$



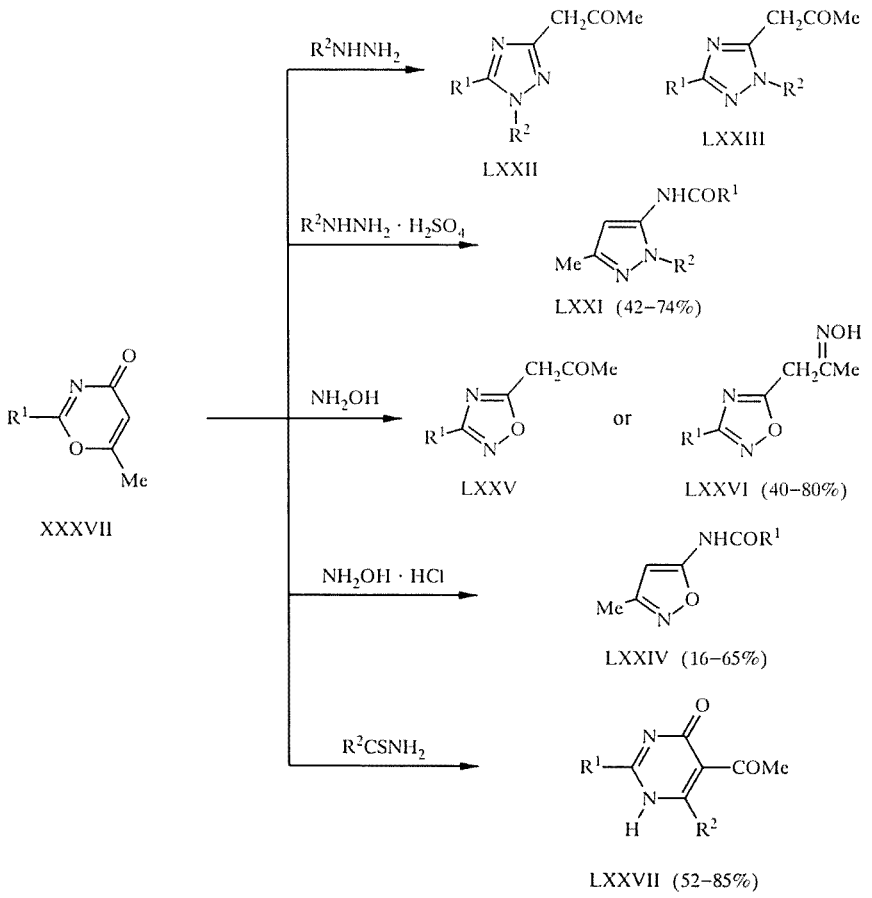
LXVI LXVIII (73–89%)

$R^1 = SCH_2COPh$; R^2 = Me, $PhCH_2$

Against a background of what has been stated, the interaction of the oxazine LXIX with ammonium acetate and a solution of ammonia in ethanol seems somewhat unusual, since instead of the expected pyrimidine derivatives it leads to 2-acetoacetylamino- and 2-methoxyamino-4-phenylthiazoles. At the same time, the reaction of this oxazine with an alcohol solution of methylamine gives the pyrimidine LXX [48].

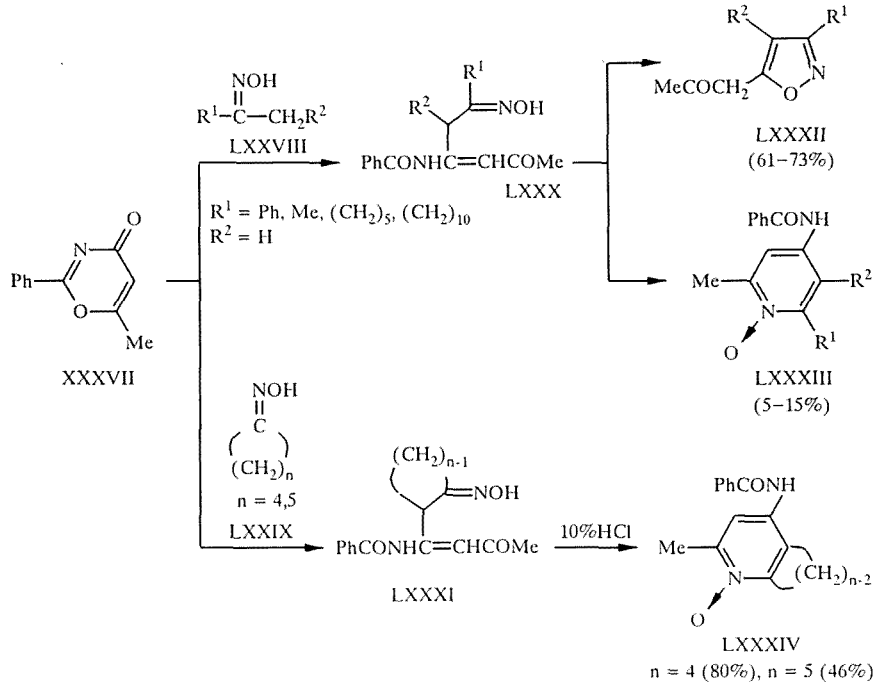


The reactions of 4-oxooxazines XXXVII with bifunctional nitrogenous nucleophiles, such as derivatives of hydrazine, hydroxylamine, or thiocarboxamide, are of great interest. From the practical standpoint, these reactions are essential as a new approach in the creation of derivatives of pyrazole (LXXI) [49], 1,2,4-triazole (LXXII, LXXIII) [49-51], oxazole (LXXIV) [52], 1,2,4-oxadiazole (LXXV, LXXVI) [52], or 4-pyrimidone (LXXVII) [50, 53, 54]. The formation of different reaction products is evidently associated with the possibility of nucleophilic attack both on C_2 and on C_6 of the heterocycle, which, in turn, is determined by the form in which the reagent reacts: in the form of a base ("weak nucleophile") or in the form of a salt ("strong nucleophile").

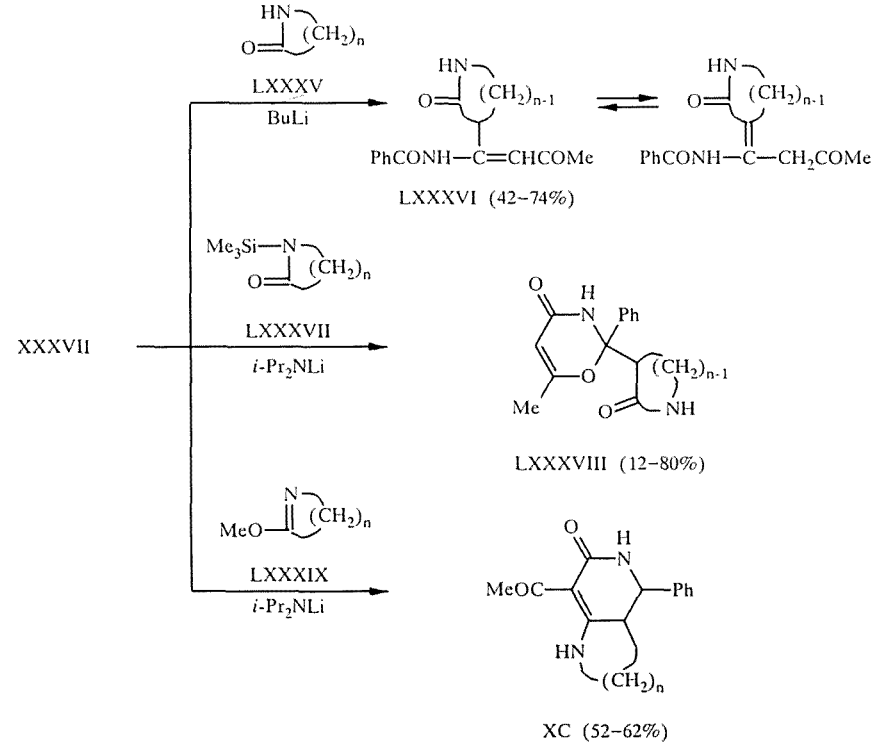


3. Reactions with C-Nucleophiles

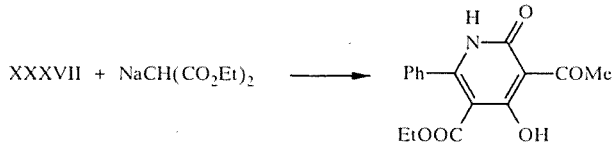
Studying the reaction of 2-phenyl-6-methyl-4H-1,3-oxazin-4-one with the oximes LXXVIII and LXXIX, the authors of [55] suggested that the nucleophilic attack is directed toward C_4 of the oxazine ring, which leads to its opening and the formation of oximes LXXX and LXXXI, which, by recyclizing, can form both izoxazoles LXXXII and N-oxides of pyridine LXXXIII, LXXXIV.



The same oxazine, reacting with lactams LXXXV in the presence of butyllithium, followed by hydrolysis with 10% HCl, gives a product of ring opening LXXXVI as a result of nucleophilic attack on C_4 of the oxazine ring. In the presence of lithium diisopropylamide, N-trimethylsilyllactams LXXXVII give products of addition to the C=N bond of LXXXVIII, while under the action of esters of lactimes LXXXIX, it is converted to 2-pyridones XC as a result of nucleophilic attack at C_2 [56, 57].



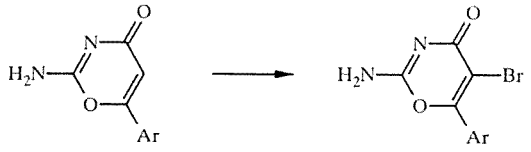
The reaction of sodium malonic ester with 2-phenyl-6-methyl-1,3-oxazin-4-one [53] may be considered as the reaction of opening of the heterocycle as a result of nucleophilic attack on C_2, followed by closing of the acyclic intermediate obtained into the pyridine derivative XCI [58].



XCI (44%)

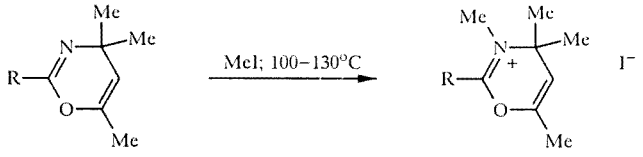
4. Reactions with Electrophilic Reagents

The classical reactions of electrophilic substitution of unsaturated 4H-1,3-oxazines in position 5, as well as alkylation and acylation of the ring nitrogen atom, are represented by only a few examples. Thus, 2-amino-6-aryl-1,3-oxazin-4-ones, when treated with a solution of bromine in chloroform in the presence of 1 N NaOH, give the corresponding 5-bromo-substituted products [41, 42].



(80%)

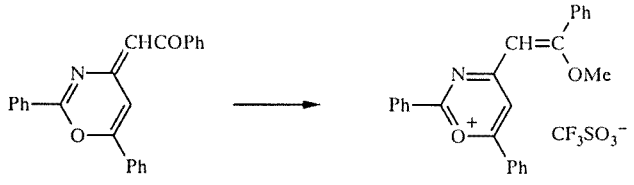
Methylation of the oxazine XXIV with methyl iodide proceeds rather complexly. Only for 2-(p-tolyl)-4,4,6-trimethyl-4H-1,3-oxazine has it been possible to isolate the N-methylation product XCII with a yield of 31% [47].



XXV XCII (31%)

R = Alk, Ar

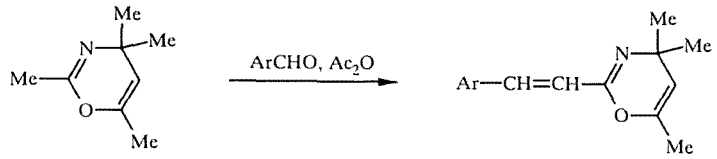
The reaction of 2,4-diphenyl-4-phenacylidene-1,3-oxazine XCIII with methyl trifluoromethanesulfonate with boiling in dichloroethane leads to the formation of 2,6-diphenyl-4-(β-methoxystyryl)-3-azapyrylium trifluoromethanesulfonate [59].



XCIII (84%)

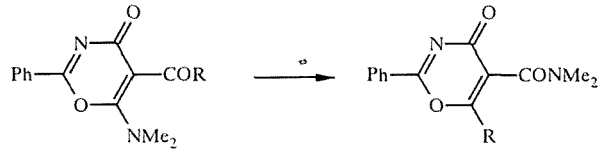
5. Other Reactions

The spectrum of these reactions is extremely broad. Thus, 2,4,4,6-tetramethyl-1,3-oxazine enters into a condensation reaction with aromatic aldehydes at the methyl group at C_2 in the presence of acetic anhydride, which is probably associated with the high electron acceptor character of this heterocycle [47].



(23–33%)

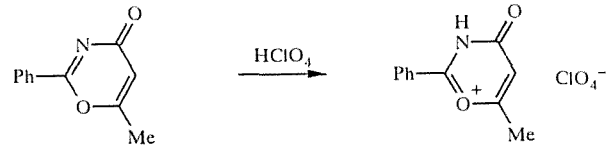
The amides XCIV are obtained in a quantitative yield when dry HCl is passed through a solution of the oxazines XLIV in anhydrous chloroform [33].



XLIV XCIV

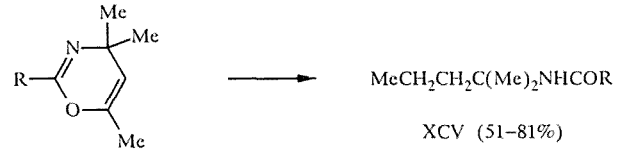
R = H, Me, MeO

2-Phenyl-6-methyl-1,3-oxazin-4-ones (XXXVII), when treated with 70% $HClO_4$, give the corresponding stable oxazinium salts [60].



XXXVII

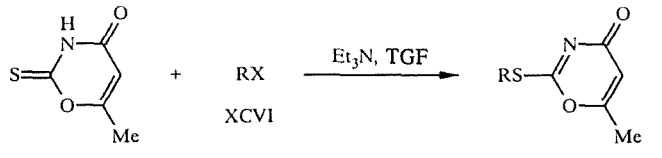
Catalytic hydrogenation of the oxazines XXV in the presence of an Adams catalyst in ethanol at atmospheric pressure leads to the amide XCV [47].



XXV XCV (51–81%)

R = Alk, Ar

In the alkylation of 2-thioxo-6-methyl-1,3-oxazin-4-one by haloderivatives XCVI, the oxazinones XCVII are formed in good yield [48, 61].



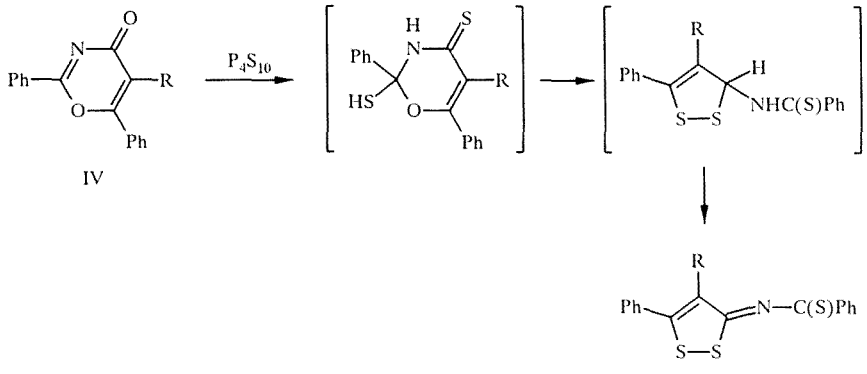
XCVII (67–77%)

R = Me, Ph, EtO_2CH_2, $PhCOCH_2$; X = I, Br

2,6-Diphenyl-4-phenacyliden-1,3-oxazine was obtained in a 72% yield from 2-phenyl-4-acylmethyl-5H-6-phenyl-3-azapyrylium hexachloroantimonate when the latter was heated to 70°C in pyridine [59].

(72%)

The reaction of oxazinones IV with P_4S_{10} in boiling xylene, leading to 5-(thiobenzoylimino)-1,2-dithiones XCVIII [4], seems rather complex. The scheme of the process proposed by these authors is quite logical, but, in our opinion, is not indisputable.

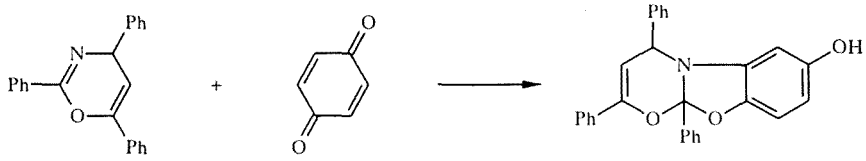


IV

R = Me, Ar

XCVIII

In dry acetone at room temperature, 2,4,6-triphenyl-1,3-oxazine, reacting with p-benzoquinone according to the [2 + 3] cycloaddition type, forms 8-hydroxy-2,4,10a-triphenyl-4H-1,3-oxazino[2,3-b]benzoxazoline in a yield of 96% [62].



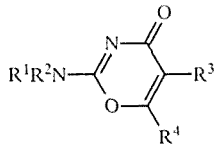
Thus, the chemical behavior of 4H-1,3-oxazines is basically determined by the nucleophilicity of the reagents. This is quite explainable, since the oxazine molecules contain three quite pronounced electrophilic centers C_2, C_4, and C_6. The selection among them in the interaction with the nucleophile is determined by the concrete nature of the interacting reagents and by the reaction conditions. The indicated reactions are not only interesting from the theoretical standpoint but also of great interest for the creation of new acyclic and cyclic systems of practical significance. Reactions with electrophilic reagents and all other properties of the oxazines under consideration occupy a more modest place and may be the objects of further investigations, which will ultimately make it possible to compile a more complete representation of this interesting class of compounds.

BIOLOGICAL ACTIVITY

Most of the studies on the biological activity of unsaturated oxoderivatives of 1,3-oxazines have been associated with "3-oxauracil" [63]. The biological activity of 4H-1,3-oxazines has received little study. However, even the few investigations permit us to hope that these compounds, which possess a broad spectrum of biological action, will take a worthy place among

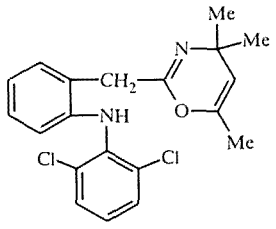
unsaturated 1,3-oxazines. In connection with this, we should mention the oxazinones XCIX, which possess immunomodulating properties [64].

2-Arylaminomethylenamino-6-aryl-1,3-oxazin-4-ones [22] possess anti-inflammatory and analgesic activity comparable with or surpassing the action of amidopyrine, and weak antimicrobial activity. Analgesic and antipyretic properties are also possessed by the 1,3-oxazine (C) [65].



XCIX

$R^1 = Alk; R^2 = Alk, Ar; R^3 = H, Alk, Ph; R^4 = H, Alk, Hal$



C

The toxicity of a broad series of 1,3-oxazines, including unsaturated ones, depends substantially on the structure [66], just as in the case of 1,3-thiazines. The same authors have shown that 4,4,6-trimethyl-2-dimethylamino-4H-1,3-oxazine has a pronounced radioprotective effect. Our investigations on the fungicidal activity of a large series of 1,3-oxazines have shown that in strength of action they significantly surpass the pyrimidine analogs [67]. Oxazines with fungicidal and analgesic effects [68] have been obtained as a production of the Wilsmayer reaction of oxazole derivatives with aldehydes.

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